UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/753851

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/753,851	12/02/96	WEINBERG	J 1579-21

EXAMINER

HM12/0530

MARY J WILSON
NIXON AND VANDERHYE
8TH FLOOR
1100 NORTH GLEBE ROAD
ARLINGTON VA 22201-4714

ART UNIT	PAPER NUMBER
1644	63

1644

DATE MAILED: 05/30/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/12/01 ; 3/23/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 9-12, 14-19, 23-25 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 9-12, 14-19, 23-25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment under Rule 1.111, filed 3/12/01 (Paper No. 61), is acknowledged.

Claims 9-12 and 14-19 and 23-25 are under consideration.

Claims 1-8, 13, 21-22 have been canceled previously

Claim 20 was not entered.

2. The text of those sections of Title 35 USC not included in this Action can be found in prior Actions.
This Office Action will be in response to applicant's arguments, filed 3/12/01 (Paper No. 61).
The rejections of record can be found in previous Office Actions.
See Paper Nos.16/22/34/38/41/46/50/55/58/60.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper No. 60.

As pointed out previously that the instant claims are free of the prior art, this Office Action will be considering both previously elected and nonelected species encompassing anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate

Therefore, claims 8-12, 14-19 and 21-25 are under consideration.

3. Formal drawings and photographs have been submitted which fail to comply with 37 CAR 1.84.
Please see the form PTO-948 previously sent in Paper No. 26.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes.

4. Claims 9-12 and 14-19 and 23-25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record set forth in Paper Nos. 46/50/55/58/60.

Applicant has not disclosed how to use CD44-specific antibodies, soluble CD44, CD44 oligopeptides and hyaluronate to inhibit HIV infection or to inhibit CD44-facilitated HIV infection therapeutically in humans. There is insufficient information or nexus of the invention with respect to the in vitro or in vivo ability of claimed therapeutic strategies to inhibit HIV infection or to inhibit CD44-facilitated entry of HIV into cells in vivo or into monocytic cells in vitro in a mixed cell population. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro inhibition of monocyte infection by a particular HIV strain (Example on page 31 of the instant specification) accurately reflects the relative efficacy of the claimed therapeutic strategies, which broadly encompass preventing or treating HIV infection, as disclosed in the specification and commensurate in scope with the claimed invention. In the absence of objective evidence commensurate in scope with the claimed methods, applicant has not provided convincing objective evidence that the claimed invention is effective as a therapeutic or preventative for HIV infection based on the in vitro inhibition of HIV infection of monocytes in vitro alone.

Applicant's arguments, in conjunction with the previously submitted Weinhold declaration under 37 C.F.R. § 1.132, filed 3/12/01 (Paper No. 61) have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.

Applicant argues that CD44 facilitates HIV infection in human cells and that CD44-specific inhibitors inhibits infection and expression.

Applicant point out that anti-CD4 antibodies block HIV infection, but that this is usually not complete and auxiliary cellular receptors for HIV have been postulated but not demonstrated.

Applicant in conjunction with Weinhold submit that the ability to block HIV infection of mononuclear phagocytes using CD44 blocking agents is of obvious significance and that mononuclear phagocytes are important target cells.

As pointed out previously, applicant continues to argue in conjunction with Weinhold that the ability of blocking HIV infection of mononuclear phagocytes using CD44 blocking agents is of obvious significance; given the importance of mononuclear phagocytes and monocytotropic stains of HIV in the transmission and spread of HIV infection. Applicant asserts that strategies that use anti-CD44 treatments would therefore target these critically important cell types.

The following of record is noted herein for convenience.

It appears that Section 5 of the Weinhold Declaration indicate that results obtained in vivo and described in this application would give little reason to doubt the effectiveness of the claimed approach.

However, the only Example disclosed in the specification as-filed relies upon in vitro infection studies. Therefore, it is not clear what in vivo studies applicant is relying upon.

While Weinhold relies upon the successful use of antibodies and soluble receptors in the treatment of inflammatory diseases such as arthritis and inflammatory bowel disease; such studies do not necessarily correlate with inhibiting CD44-facilitated HIV infection as it reads on in vivo therapy of treating HIV infections, as encompassed by the claimed methods. Applicant's reliance upon other therapeutic methods rely upon pathological conditions that differ in etiologies and, in turn, rely upon different ingredients, process steps and therapeutic endpoints than that encompassed by the claimed methods.

While anti-CD44 antibodies may have been able to reduce inflammation in mice, which relies upon inhibiting leukocyte adherence; the instant claims encompass inhibiting HIV infection. The nature as the mechanisms of action of the disease states or conditions differ.

In contrast to applicant's assertions or record, the skilled artisan as well as the rejection of record were well aware of the lack of correlation or predictability between in vitro and animal models and methods of reducing or inhibiting HIV infection, particularly in vivo at the time the invention was made.

With respect to the inquiry about Rivadeneira et al. (Aids Research and Human Retroviruses 11: 541-546, 1995); the following is noted.

It is noted that CD44-specific antibodies can block HIV infection of mononuclear phagocytes in vitro, however these same antibodies can not block the infection of mitogen-stimulated lymphocytes or cells of a T lymphocyte line in vitro (Rivadeneira et al., Aids Research and Human Retroviruses 11: 541-546, 1995; see entire document including Abstract; of record).

Therefore, CD44-specific inhibitors appear to inhibit HIV infection in mononuclear phagocytes under in vitro defined conditions but cannot inhibit HIV infection in other cell types (e.g. lymphocytes); wherein said other cell types such as lymphocytes are involved in HIV infection and transmission.

As acknowledged out in the Introduction of Rivadeneira et al.; I has been well known in the art that cellular CD4 has been recognized as the predominant membrane protein that interacts with HIV. However, it has been well known that HIV infection occurs in cells that express variable or no detectable levels of CD4. It has been well known that $CD4^+$ T cells are the primary target of HIV infection both in vitro and in vivo.

Therefore, it would not have been predictable that targeting CD44 in mononuclear phagocytes with CD44-specific inhibitors would affect or inhibit HIV infection of susceptible cell populations either in vitro or in vivo; wherein said susceptible or infected cell populations comprise lymphocytes that are not targeted by CD44-specific inhibitors and that HIV infection and transmission would occur via CD4, wherein said CD4 is not targeted by CD44-specific inhibitors.

While certain adhesion molecules may play a role as a coreceptor of HIV-1 or the infection or spread of HIV-1 ; CD44--specific inhibitors appear limited in their ability to their ability to suppress infection, as encompassed by the claimed methods which involve in vivo administration including treating infected individuals.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to suppress the infection of leukocytes with HIV wherein said method comprises administering to a subject exposed to or infected by HIV, including the use of adhesion-based reagents, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for suppressing HIV infection in vivo.

As pointed out previously; applicant's arguments of record have not been found persuasive and the rejection is maintained.

It has been noted that if applicant limits claims to the in vitro inhibition of HIV infection of mononuclear phagocytes or monocytes, then the rejection under 35 U.S.C. § 112, first paragraph would be withdrawn.

5. Claims 14-19 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "The disclosed and claimed agents (anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate) to inhibit HIV infection of mononuclear phagocytes (versus a mixed cell population) in vitro; does not reasonably provide enablement for any "agent that binds CD44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 3/12/01 (Paper No. 61) have been fully considered but are not found convincing for the reasons of record.

Applicant argues that the claims are drawn to methods of inhibiting CD44-facilitated HIV infection of a method of inhibiting CD44-facilitated HIV infection of a mononuclear phagocyte and not drawn to an agent that binding CD44 molecules present on the cell surface.

Applicant asserts that given the nature of the contribution of the applicant's discovery; it is entirely appropriate that they be entitled to a method claimed that covers the use of any and all agents that bind CD44 and in so doing block HIV infection.

The examiner's rebuttal are essentialy the same as of record and reiterated herein for applicant's convenience.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "agents that bind CD44" other than those encompassed by "anti-CD44 antibodies, soluble CD44, CD44 oligopeptides and hyaluronate".

An alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property (e.g. structural or functional). Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed ligands in manner reasonably correlated with the scope of the claims to stimulate T cells response to transfected tumor cells.

Further, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Therefore, structurally unrelated compounds encompassed by the claimed "agents that bind CD44" would be expected to have greater differences in their activities.

Here applicant has not provided the defining structural or correlative teachings sufficient to enable one of skill to isolate and identify the "agents" with the appropriate structural characteristic or property of the instant "agents" to the extent that one of skill would be able to predictably identify the claimed "ligands". It is noted that the known anti-CD44 agents indicated herein differ with respect to structure to the extent that the skilled artisan would not envision one in view of the other. Even those these ligands have overlapping functional properties, these ligands differ with respect to structure and function.

Since the disclosure fails to describe the common structural attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a limited number of ligands and the ability to screen, is insufficient to enable the genus, encompassed by the claimed invention.

The problem of predicting protein structure from such limited information of a limited number of known ligands protein and, in turn, utilizing predicted structural determinations to ascertain functional aspects of other ligands, including unknown ligands and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

In addition, the issues concerning the lack of predictability of inhibiting HIV with different reagents as well as with different anti-adhesion molecule agents are addressed above in Section 6.

Insufficient direction or guidance is provided to assist one skilled in the art in the selection of any "anti-CD44 agent" other than those disclosed in the specification as filed nor is there evidence provided that other such "anti-CD44 agent" can inhibit HIV infection of monocytes in vitro. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, making and using "anti-CD44 agents that inhibit HIV infection of

mononuclear cells would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant's arguments are not found persuasive.

6. No claim is allowed.

It has been noted that claims drawn to methods of inhibiting HIV infection of mononuclear phagocytes (versus a mixed cell population) in vitro with CD44-specific antibodies would be considered allowable.

As indicated previously, it has been noted that applicant has clearly stated that the instant invention is not drawn to the use of CD44-specific immunotoxins and that the current claimed recitation supports this conclusion.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

PHILLIP GAMBEL

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
May 29, 2001